REMARKS

Claims 2, 8, 9, 11-19, 21-25, 27-29, 31-42, and 47-65 presently appear in this case. No claims have been allowed. Claims 2-6, 9, 15-19, 21, 23, 26-29, 32, 38-42 and 45 have been withdrawn from consideration. The official action of April 21, 2003, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to technology developed in the laboratory of the present inventors, which is now known in the art as autoimmune neuroprotection. It has been discovered that neuronal degeneration caused by the neurodegenerative effects of disease or secondary neuronal degeneration that follows the primary neuronal damage of an injury can be reduced if steps are taken to cause T cells activated against an NS-specific antigen which, in its native state, is present at the site of neuronal degeneration, to accumulate at the site of neuronal degeneration. The mere presence of these activated T cells at the site of injury causes a cytokine response that has a significant effect in reducing the neuronal degeneration. The present invention is directed to the improvement in which the T cells are activated by Copolymer 1 or a Copolymer 1-related peptide or polypeptide. The preferred methods of causing the T cells to accumulate at the site of injury is to either administer T

cells activated against Copolymer 1 or Copolymer 1-related peptide or polypeptide, or to administer the Copolymer 1 or a Copolymer 1-related peptide or polypeptide itself in such a way as to cause a T cell response such that T cells become activated against Copolymer 1 or a Copolymer 1-related peptide or polypeptide.

The interview among examiners, Bunner and Kunz, the inventor, Prof. Michal Schwartz, and the undersigned attorney, which interview was also attended by examiners Turner, Nichols, and Kemmerer, on June 26, 2003, is hereby gratefully acknowledged. In this interview, Prof. Schwartz presented a slide presentation explaining the work of her laboratory that resulted in the present invention and the subsequent work which has been done in proving broad applicability of the present invention. This work has been published in prestigious journals, copies of which are being made of record herewith. Claim wording that might appropriately claim the full breadth of this invention without reading on the prior art and in full compliance with 35 USC 112 was discussed at the interview. While no agreements were reached, it is believed that the examiners now have a better understanding of the present invention, and that in additional discussions, the examiners can help applicants in appropriate wording of the

claims in order to obtain appropriate protection for this important and novel advance in the art.

The claims in this application have now been substantially revised. The new and amended claims submitted herewith attempt to adopt the language that was discussed at the interview. If this language is not considered to put this case into condition for allowance, it is respectfully requested that the examiner contact the undersigned to schedule a further interview to discuss language for this case that might be acceptable.

Support for the language of new claims 47 and 51 may be found in the specification. For example, the paragraph bridging pages 12 and 13 discloses that the invention may be used to inhibit the degenerative effects of disease in the NS, including the inhibition of secondary degeneration that may otherwise follow primary NS injury. With respect to claim 51, note page 12, lines 22-23, which states that the present invention relates to methods to "ameliorate ... the effects of injury to or disease of, the nervous system".

The examiner has deemed the previous restriction requirement to be proper and has made it final.

It is urged that new claims 47 and 51 are linking claims that appropriately claim the full breadth of the method of the present invention. The main step of both claims is

causing T cells activated by Copolymer 1 or a Copolymer 1-related peptide or polypeptide to accumulate at the site of neuronal degeneration in the individual in need, thereby reducing neuronal degeneration at that site, or ameliorating the effects of the injury or disease at that site. This is generic to preferred methods of active and passive administration of such T cells as claimed in claims 49, 50, 60 and 62. Furthermore, as was explained in the interview, the effect of the invention is the same whether treating secondary degeneration caused by an injury or the degeneration caused by a disease. Accordingly, it is again respectfully requested that the restriction requirement be reconsidered and withdrawn in view of the presence of the linking claims submitted hereby.

It is noted that the requirement for a title change has been maintained and held in abeyance until all other issues are resolved.

It is noted that the objection to claims 1, 8, 10, 20, 22, 30-31, 33, 43-44 and 46 for reciting non-elected species and groups has been maintained and held in abeyance until the elected species are found allowable.

Claims 1, 7-8, 10-14, 20, 22, 24-25, 30-31, 33-37, 43-44 and 46 have been rejected under 35 USC 112, first paragraph, because the specification, while being enabling for

a method of inhibiting secondary neuronal degeneration of ganglion cells caused or exacerbated by glutamate toxicity in the CNS by administering to a person with glaucoma an effective amount of COP 1 to inhibit secondary neuronal degeneration, does not reasonably provide enablement for preventing or inhibiting neuronal degeneration, promoting nerve regeneration or protecting CNS or PNS cells from glutamate toxicity. The examiner states that the specification does not enable persons of ordinary skill in the art to make or use the invention commensurate in scope with these claims. This rejection is respectfully traversed.

Prof. Schwartz made a comprehensive presentation at the interview explaining the many successful experiments which have been undertaken in her laboratory to show the broad applicability of the technology involved with the present invention. While much of the background and most of the experiments dealt with T cells activated against Cop 1, some of it deals with other activated T cells. However, that which is now known about this technology allows one of ordinary skill in the art to understand that the predictions made in the present specification would be expected to be accurate.

Attached hereto are the following thirty-eight references from the laboratory of the present inventors relating to the technology behind the present invention:

YOLES et al., "Degeneration of Spared Axons Following Partial White Matter Lesion: Implications for Optic Nerve Neuropathies", *Experimental Neurology*, 153:1-7 (1998)

MOALEM et al., "Autoimmune T Cells Protect Neurons from Secondary Degeneration after Central Nervous System Axotomy", *Nature Medicine*, 5:49-55 (1999)

SCHWARTZ et al., "Innate and Adaptive Immune Responses Can Be Beneficial for CNS Repair", *TINS*, 22:295-299 (1999)

SCHWARTZ, "Vaccination for T Cell-Mediated Neuroprotection: Dream or Reality?", *Drug Development Research*, 50:223-225 (2000)

HAUBEN et al., "Autoimmune T Cells as Potential Neuroprotective Therapy for Spinal Cord Injury", *The Lancet*, 354:286-287 (2000)

SCHWARTZ et al., "Neuroprotection: A New Treatment Modality for Glaucoma?", *Current Opinion in Ophthalmology*, 11:107-111 (2000)

KIPNIS et al., "T Cell Immunity to Copolymer 1 Confers Neuroprotection on the Damaged Optic Nerve: Possible Therapy for Optic Neuropathies", *PNAS*, 97:7446-7451 (2000)

MOALEM et al., "Autoimmune T Cells Retard the Loss of Function in Injured Rat Optic Nerves", *Journal of Neuroimmunology*, 106:189-197 (2000)

HAUBEN et al., "Passive or Active Immunization with Myelin Basic Protein Promotes Recovery from Spinal Cord Contusion", *The Journal of Neuroscience*, 20:6421-6430 (2000)

MOALEM et al., "Production of Neurotrophins by Activated T Cells: Implications for Neuroprotective Autoimmunity", *Journal of Autoimmunity*, 15:331-345 (2000)

SCHWATRZ, "T Cell Mediated Neuroprotection is a Physiological Response to Central nervous System Insults", *J Mol Med*, 78:594-597 (2001)

FISHER et al., "Vaccination for Neuroprotection in the Mouse Optic Nerve: Implications for Optic Neuropathies", *The Journal of Neuroscience*, 21:136-142 (2001)

SCHWARTZ et al., "Beneficial Immune Activity after CNS Injury: Prospects for Vaccination", *Journal of Neuroimmunology*, 113:185-192 (2001)

BUTOVSKY et al., "Morphological Aspects of Spinal Cord Autoimmune Neuroprotection: Colocalization of T Cells with B7-2 *(CD86)* and prevention of Cyst Formation", *The FASEB Journal*, express article 10.1096/fj.00-0550fje, published online February 26, 2001

SCHORI et al., "Vaccination for Protection of Retinal Ganglion Cells Against Death from Glutamate Cytotoxicity and Ocular Hypertension: Implications for Glaucoma", *PNAS*, 98:3398-3403 (2001)

YOLES et al., "Self-Protection Mechanism Awakened by Glutamate in Retinal Ganglion Cells", *Journal of Neurotrauma*, 18:339-349 (2001)

YOLES et al., "Protective Autoimmunity Is a Physiological Response to CNS Trauma", *The Journal of Neuroscience*, 21:3740-3748 (2001)

SCHWARTZ et al., "Protective Autoimmunity: Regulation and Prospects for Vaccination after Brain and Spinal Cord Injuries", *TENDS in Molecular Medicine*, 7:252-258 (2001)

KIPNIS et al., "Neuronal Survival after CNS Insult Is Determined by a Genetically Encoded Autoimmune Response", *The Journal of Neurosciences*, 21:4564-4571 (2001)

HAUBEN et al., "Posttraumatic Therapeutic Vaccination with Modified Myelin Self-Antigen Prevents Complete Paralysis While Avoiding Autoimmune Disease", *The Journal of Clinical Investigation*, 108:591-599 (2001)

FISHER et al., "Increased Post-traumatic Survival of neurons in IL-6-Knockout Mice on a background of EAE Susceptibility", *Journal of Neuroimmunology*, 119:1-9 (2001)

SCHORI et al., "T-Cell-Based Immunity Counteracts the Potential Toxicity of Glutamate in the Central Nervous System", *Journal of Neuroimmunology*, 119:199-204 (2001)

HAUBEN et al., "Vaccination with a Nogo-A-Derived Peptide after Incomplete Spinal-Cord Injury Promotes Recovery Via a T-Cell-Mediated Neuroprotective Response: Comparison with Other Myelin Antigens", *PNAS*, 98:15173-15178 (2001)

SCHWARTZ et al., "Differing Views on Spinal Cord Repair", *Science*, 296:1400 (2002)

KIPNIS et al., "Dual Action of Glatiramer Acetate (Cop-1) in the Treatment of CNS Autoimmune and Neurodegenerative Disorders", *TRENDS in Molecular Medicine*, 8:319-323 (2002)

SCHORI et al., "Immune-Related Mechanisms Participating in Resistance and Susceptibility to Glutamate Toxicity", *European Journal of Neuroscience*, 16:557-564 (2002)

BAROUCH et al., "Autoreactive T Cells Induce Neurotrophin Production by Immune and Neural Cells in Injured Rat Optic Nerve: Implications for Protective Autoimmunity", *The FASEB Journal*, 16:1304-1306 (2002)

KIPNIS et al., "Myelin Specific Th1 Cells Are Necessary for Post-Traumatic Protective Autoimmunity", *Journal of Neuroimmunology*, 130:78-85 (2002)

SCHORI et al., "Severe immunodeficiency Has Opposite Effects on Neuronal Survival in Glutamate-Susceptible and -Resistant Mice: Adverse Effect of B Cells", *The Journal of Immunology*, 169:2861-2865 (2002)

SCHWARTZ et al., "Multiple Sclerosis as a By-Product of the Failure to Substain Protective Autoimmunity: A Paradigm Shift", *The Neuroscientist*, 8:405-413 (2002)

HAUBEN et al., "Sexual Dimorphism in the Spontaneous Recovery from Spinal Cord Injury: A Gender Gap in beneficial Autoimmunity?", *European Journal of Neuroscience*, 16:1731-1740 (2002)

MIZRAHI et al., "The Tissue-Specific Self-Pathogen Is the Protective Self-Antigen: The Case of Uveitis", *J Immunol*, 169:5971-5977 (2002)

KIPNIS et al., "Neuroprotective Autoimmunity: Naturally Occurring $CD4^+CD25^+$ Regulatory T Cells Suppress the Ability to Withstand Injury to the Central Nervous System", *PNAS*, 99:15620-15625 2002)

SCHWARTZ et al., Autoimmunity on Alert: Naturally Occurring Regulatory $CD4^+CD25^+$ T Cells as Part of the Evolutionary Compromise Between a 'Need' and a 'Risk", *TRENDS in Immunology*, 23:530-534 (2002)

HAUBEN et al., "Therapeutic vaccination for Spinal Cord Injury: Helping the Body to Cure Itself", *TRENDS in Pharmacological Sciences*, 24: 7-12 (2003)

SCHWARTZ, "Macrophages and Microglia in Central Nervous System Injury: Are They Helpful or Harmful?", *Journal of Cerebral Blood Flow & Metabolism*, 23:358-394 (2003)

ANGELOV et al., "Therapeutic Vaccine for Acute and Chronic Motor Neuron Diseases: Implications for Amyotrophc Lateral Sclerosis", *PNAS*, 100:4790-4795 (2003)

SCHWARTZ et al., "Protective Autoimmunity Against the Enemy Within: Fighting Glutamate Toxicity", *Trends Neurosci*, 26:297-302 (2003)

The basic paper is Moalem et al, Nature (1999). Halben, J. Neurosci. (2000) expands the original work in the optic nerve to spinal cord contusion, including both active and passive administration. This proves the concept that the same active T cells work in radically different sites. Fisher et al, J. Neurosci. (2001), disclose active and passive vaccination to raise T cells specific to various NS-specific proteins. Butovsky et al, FASEB J (2001), show a proof of mechanism establishing that T cells get to the site of the lesion in the spinal cord. Schori et al, PNAS (2001), is an important paper relating to glutamate and glaucoma, establishing that COP 1 works where there is no myelin and MBP does not work. Yoles et al, J. Neurosci. (2001), shows the beneficial aspect of passive transfer of T cells. Hauben et al, J.C.I. (2001), disclose experiments that altered peptides

work in order to obtain the benefit of neuroprotection. It should be understood that this paper won an award as one of the ten leading papers of the year for this journal. Hauben et al, PNAS (2001), shows active and passive vaccination with Nogo A. Misrachi et al, J. Immunol. (2002), is important in showing that the specificity of the antigen for beneficial autoimmunity is determined by the site and not by the type of insult. Angelov et al, PNAS (2003), shows the operability of the present invention in the PNS.

It is urged that these papers establish for the record what Prof. Schwartz was able to explain at the interview. In light of all the experiments that have been done with respect to the technology of this invention, the full scope of the present invention would be expected to be operable. There is no reason to believe that undue experimentation would be involved in order to make and use the full scope of the present invention. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

The art made of record by the examiner has been noted, as has the examiner's implicit recognition that none are sufficiently pertinent to warrant their application against the claims.

Claims 22, 24-25 and 43-44 have been rejected under 35 USC 112, second paragraph as being indefinite. This rejection is respectfully traversed.

The independent claims previously in the case have now been deleted and all of the claims have been substantially amended. It is not believed that any of the grounds of indefiniteness noted by the examiner with respect to this rejection are applicable to the new claims. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 22, 24-25 and 43-44 have been rejected under 35 USC 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. This rejection is respectfully traversed.

Claims 44-46 have now been deleted. New claims 47 and 51 have as their main step "causing T cells activated by Copolymer 1 or a Copolymer 1-related peptide or polypeptide to accumulate at the site of neuronal degeneration in the individual in need ...." Claim 49 specifies that the T cells are caused to accumulate at the site of neuronal degeneration by administering an effective amount of Copolymer 1 or a Copolymer 1-related peptide or polypeptide, and claim 50 specifies that the activated T cells are caused to accumulate at the site of neuronal degeneration by administering an

effective amount of T cells. One does not look to the claims to find out how to practice the invention they define, but to the specification. See *In re Johnson* 194 USPQ 187, 195 (CCPA 1977). It is a function of the claims to specify what applicant considers to be the invention.

No essential step is omitted, as the only essential step is causing the T cells to accumulate at the site of neuronal degeneration, as was explained in detail in the interview. Certainly the administration of activated T cells is not an essential step for causing T cells to accumulate at the site of injury. It is not essential because the T cells can be caused to accumulate at the site of injury by administration of antigen in such a way as to cause T cells to accumulate at the site of injury. No essential step has been omitted. Nothing else is needed in order to reduce neuronal degeneration caused by the neurodegenerative effects of disease or to reduce secondary neuronal degeneration that follows the primary neuronal damage of an injury other than causing T cells to accumulate at the site of neuronal degeneration. Claim 50, which specifies that activated T cells are administered, does not add a step to claim 47, but further defines the causing step. Breadth is not tantamount to indefiniteness. See *Ex parte Clark*, 174 USPQ 40, 42 (Bd.

App. 1971). Reconsideration and withdrawal of this rejection is therefore respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record, and fully comply with 35 USC 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By _____
Roger L. Browdy
Registration No. 25,618

RLB:gkw
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\B\BENA\Eis-Schwartz18\Pto\AmendmentC.doc